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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/981,845
Filing Date: October 18, 2001
Appellant(s): ASHKAR *ET AL.*

Patrea Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12 June 2006 appealing from the Office action mailed 08 August 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter in the brief is essentially correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The Examiner relies upon the evidence submitted by Appellant, specifically Hu *et al.*, J. Biol. Chem. 270(44):26232-26238 (1995) and Tuck *et al.*, J. Cell. Biochem. 78:465-475 (2000).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

an active osteopontin peptide fragment comprising the amino acid of SEQ ID NO:11 wherein the peptide binds to **αvβ3 integrin receptor** on a cell surface and increases cell attachment and increases cell spread of **osteoprogenitor cells,**

does not reasonably provide enablement for:

an active osteopontin peptide fragment comprising the amino acid of SEQ ID NO:11, wherein the peptide binds to a least one integrin receptor on a cell surface selected from the group consisting of **αvβ5, 4β1, 2β1, VCAM, ICAM CD44, V3Vx** and increases cell attachment and increases cell spread of cells selected from the group consisting of **tumor cells, macrophages, periosteal cells, endothelial cells, epithelial cells, eosinophils, stem cells, limited potential precursor cells, precursor cells,**

committed precursor cells, and differentiated cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The purported utility of the instant invention is osseointegration of an implant into the surrounding tissues. Osseointegration is the growth action of bone tissue, as it assimilates surgically implanted devices or prostheses to be used as either replacement parts (such as hip replacement) or as anchors (such as dental implants). Implants coated with the claimed osteopontin peptide fragments should bind receptors supportive of osteoblast function in order to make successful bone implants. The specification teaches that when plates are coated with the claimed osteopontin peptide fragments, human osteoprogenitor cells undergo a transformation from a neutral to a proactive condition in which the number of attached cells, as well as percentage spread, increases (specification, page 53, line 5-page 55). The instant specification teaches SEQ ID NO:11 as an osteopontin-derived fragment with cell attachment and cell spread activity (page 7, lines 23-27 and page 8, lines 11-20). In addition, the instant specification teaches that SEQ ID NO:15 was able to accelerate the healing of dental implants in a canine animal model, thus demonstrating osseointegration (specification, page 49-53).

The scope of patent protection as defined by the claims fails to bear a reasonable correlation with the scope of enabling disclosure set forth in the specification. The specification discloses that when plates are coated with the claimed osteopontin peptide fragments, **only human osteoprogenitor cells (not any cell type)**

attach and spread to the surface (Emphasis added). Thus human osteoprogenitor cells have a receptor which recognizes the claimed osteopontin peptide fragments, causing the human osteoprogenitor cells to attach and spread to the coated surface. The specification teaches that only antibodies to $\alpha_v\beta_3$ integrin significantly diminished SEQ ID NO:15 from binding to osteoprogenitor cells (thus indicating that SEQ ID NO:15 binds $\alpha_v\beta_3$ integrin receptors on osteoprogenitor cells). The specification never discloses which integrin receptor binds SEQ ID NO:11. Neither the art of record or the instant specification teach osseointegration activity in other cell types. Neither the art of record or the instant specification teach other integrin receptors on osteoprogenitors which could induce osseointegration. Osteopontin-derived peptide fragments can not bind any type of integrin receptor on any type of cell and induce osseointegration. Hu *et al.* (reference submitted by Appellant, J. Biol. Chem. 270(44):26232-26238, 1995) teach that osteopontin (**not SEQ ID NO:11 or SEQ ID NO:15) binds integrin receptors $\alpha_v\beta_3$, $\alpha_v\beta_1$ and $\alpha_v\beta_5$, not all of the integrins as recited in instant claim 1** (Emphasis added). Tuck *et al.* (reference submitted by Appellant, J. Cell. Biochem. 78:465-475, 2000) teach that osteopontin binds $\alpha_v\beta_3$ in the MDA-MB-435 cell line **but does not bind** $\alpha_v\beta_3$ in the 21PT and 21NT cell lines (Emphasis added). It would require an indeterminate quantity of unpredictable investigational experimentation of the skilled artisan to determine which integrin receptor bound the claimed osteopontin peptide fragments, then discern which cell type expressed that specific receptor and if that cell type was conducive to osseointegration activity. Without sufficient guidance, the amount

of experimentation would be undue for one skilled in this art. Thus only osteoprogenitor cells and $\alpha v\beta 3$ integrin receptors meet the limitations of the instant claims.

Due to the large quantity of experimentation necessary to demonstrate that an active osteopontin peptide fragment comprising the amino acid of SEQ ID NO:11 can regulate cell attachment/cell spreading and induce osseointegration by binding *any integrin receptor on any cell type*, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite function limitations requirements of integrin receptors and cell types, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(10) Response to Argument

A. Claim Rejections Under 35 U.S.C. 112, First Paragraph

At page 5 of the Brief, Appellant states that the primary challenge faced in the fabrication of new implants is to increase the rate of osseointegration and the percentage of bone apposition. An enhance rate of osseointegration and/or augmented percentage of bone apposition around implants increases implanted placement indications and expedites loading time. Appellant states that recent studies have focused on improving osseointegration of implants by coating the surface with various substances including bone morphological proteins with varying degrees of success. At the bottom of page 5 to page 7 of the Brief, Appellant cites case law and discusses the

legal standard for enablement. At the middle of page 7 of the Brief, Appellant states, "as long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied". At the top of page 8 of the Brief, Appellant states that the issue is whether it would require undue experimentation to identify and make peptides having the claimed sequence. At the middle of page 8 of the Brief, Appellant argues that it is well know in the art that osteopontin binds to more than one integrin receptor, as is exemplified by Hu *et al.,* J. Biol. Chem. (reference of record). Appellant states that SEQ ID NO:11 and 15 have conserved domains similar to osteopontin. Appellant argues that the ability of the peptides recited in claim 1 to bind to at least one integrin receptor on the cell surface is demonstrated by the ability of anti-integrin antibodies to inhibit cell attachment (for example, SEQ ID NO:15, specification; Table 8). Appellant contends that this example clearly demonstrates that the claimed peptides do indeed bind to integrins.

Appellant's arguments have been fully considered, but are not deemed persuasive for the following reasons. The instant specification fails to disclose at least one method of making and using the claimed invention that bears **a reasonable correlation to the entire scope of the claim** (Emphasis added). The instant claims encompass a genus of diverse cells and integrins for osseointegration activity, while the specification discloses one type of cell (osteoprogenitor cells) and one type of integrin ($\alpha v\beta 3$ integrin receptor). Contrary to Appellant's assertion, the issue **IS NOT** whether it would require undue experimentation to identify and make peptides having the claimed

sequence. The issue is whether it would require undue experimentation to identify any type of cell expressing any type of integrin receptor which could bind the claimed peptides and induce osseointegration. Hu *et al.* teach that osteopontin (**not SEQ ID NO:11 or SEQ ID NO:15**) **binds integrin receptors $\alpha_v\beta_3$, $\alpha_v\beta_1$ and $\alpha_v\beta_5$, not all of the integrins as recited in instant claim 1** (Emphasis added). Furthermore, the specification teaches that only antibodies to $\alpha_v\beta_3$ integrin significantly diminished SEQ ID NO:15 from binding to osteoprogenitor cells (specification page 53, lines 17-21 and page 54). The specification never disclosed which integrin antibody would inhibit SEQ ID NO:11 from binding. The Examiner agrees that the claimed osteopontin peptide fragments can bind **only specific integrin receptors** (Emphasis added).

At page 9 of the Brief, Appellant argues that there is no legal requirement that the claimed peptides bind all integrins or all cell types for the peptides to have the specified utility. Appellant contends that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112, is satisfied. Appellant states that since the sequences which are responsible for binding as claimed are described, no undue experimentation would be required. Appellant argues that the claims which recite that peptides SEQ ID NOs. 7-15 bind to at least one integrin receptor on a cell surface selected from the group of receptors (as recited in claims 1, 3 and 5) are enabled.

Appellant's arguments have been fully considered, but are not deemed persuasive for the following reasons. Contrary to Appellant's assertion, the instant

specification fails to disclose at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. The breadth of the instant claims must be considered (i.e. In re Wands). The evidence does not show that a skilled artisan would have been able to carry out the steps required to practice the full scope of the claims which encompass discerning whether all of the diverse cells types (as recited in claim 6) express the integrin receptors (as recited in claim 1), and can bind the claimed osteopontin peptide fragments and induce osseointegration. There is no predictability as to which integrin receptor would bind SEQ ID NO:11 (or the other claimed osteopontin peptide fragments) because the specification only discloses that $\alpha_v\beta_3$ integrin receptors bind SEQ ID NO:15. There is no predictability as to which cell type is capable of osseointegration because the specification only discloses that osteoprogenitor cells have this activity. The specification fails to teach which integrin receptor would bind SEQ ID NO:11 or the other osteopontin peptide fragments recited in claim 1. The specification fails to teach other cell types which induce osseointegration. Table 8 (instant specification) demonstrates an 87% and 89% spread of osteoprogenitor cells in the presence of anti-CD44 and anti-$\alpha\beta1$ antibodies, respectively, compared to only a 12% spread in the presence of anti-$\alpha_v\beta_3$ antibodies. The data suggests that SEQ ID NO:15 predominantly binds integrin receptor $\alpha_v\beta_3$ in osteoprogenitor cells. The specification never tested the other integrin receptors recited in claim 1 ($\alpha v\beta5$, $4\beta1$, $2\beta1$, VCAM, V3Vx). The Examiner understands that the purported utility of the instant application is the successful osseointegration of an implant into the surrounding tissues. Implants coated with the

claimed osteopontin peptide fragments should bind receptors supportive of osteoblast function. The instant specification demonstrates that SEQ ID NO:15 binds integrin $\alpha_v\beta_3$ on osteoprogenitor cells. No integrin receptor has been taught for elected species SEQ ID NO:11 or the other osteopontin peptide fragments recited in claim 1. No other cell types that have osseointegration activity have been taught.

At page 10 of the Brief, Appellant discusses integrins. Appellant states that osteopontin will bind to different cell types that express its receptors as evidenced by Hu *et al.* (reference of record) and Tuck *et al.* J. Cell. Biochem. (reference of record). Appellant argues that Hu *et al.* employ carcinoma cells and Tuck *et al.* employ epithelial cells. Appellant maintains that the references demonstrate that osteopontin will bind to at least one of its receptors on a cell expressing the receptor. Appellant argues that since the claimed active osteopontin peptide fragments bind integrins and since integrins are expressed on diverse cells types, the claimed peptide should bind diverse cell types expressing integrins. Appellant argues that the specification describes a number of cell types that may be regulated by using the active osteopontin peptide fragments. At page 11 of the Brief, Appellant argues that the only conclusion that can be drawn from Table 8 is that cell attachment and spread are not predominantly controlled by CD44 and β1. Appellant discusses the data of Tuck *et al.* and Hu *et al.* Appellant argues that the references in combination demonstrate that osteopontin or any peptide capable of binding to osteopontin receptors can perform the same biological function in different cell types depending on the receptor predominately expressed by that cell. At the bottom of page 11 to the top of page 12 of the Brief, Appellant argues that Table 8

(in the instant specification) demonstrated an 87% and 89% spread of osteoprogenitor cells in the presence of anti-CD44 and anti-β1 antibodies, not a 100% spread. Appellant argues that the results do not exclude the fact that osteopontin can bind more than one integrin receptor, or that the effect could be concentration dependent. Appellant argues that osteoprogenitor cells express different integrins at different levels. At the middle of page 12 of the Brief, Appellant states that Horton, Int. J. Biochem. Cell. Biol. (reference of record) teach that $\alpha_v\beta_3$ expression has been shown in numerous cell types. Appellant argues that there are art recognized techniques for determining the integrin expression profile of a cell and that a patent need not teach and preferably omits what is well known in the art.

Appellant's arguments have been fully considered, but are not deemed persuasive for the following reasons. The instant invention is drawn to osteopontin peptide fragments which induce osseointegration of implants into the surrounding tissue. **The biological function of the instant peptide is osseointegration, not just attaching and spreading** (Emphasis added). **Osseointegration is the growth action of bone tissue,** as it assimilates surgically implanted devices or prostheses to be used as either replacement parts or as anchors (Emphasis added). Osteoprogenitor cells are cells that differentiate into osteoblast (cells which aid in the development of teeth and bone). The Examiner made a scope of enablement rejection based on the overwhelming scientific evidence. Only specific cell types and certain integrin receptors are enabled for the instant invention. As was stated above, the purported utility of the instant application is the successful osseointegration of an implant into the surrounding

tissues. Material surfaces that cannot bind the macromolecules supportive of osteoblast function are not likely to make successful bone implants (see specification, page 5, lines 1-15). Even if osteoprogenitor cells express different integrins at different levels, one skilled in the art would understand that $\alpha_v\beta_3$ integrins are the receptors responsible for the attachment, spread and osseointegration activity. The specification teach that SEQ ID NO:15 binds integrin $\alpha_v\beta_3$ on osteoprogenitor cells. No integrin receptors have been taught for elected species SEQ ID NO:11 or the other osteopontin peptide fragments recited in claim 1. The other integrin receptors recited in claim 1 ($\alpha v\beta 5$, $4\beta 1$, $2\beta 1$, VCAM, V3Vx) were not tested. The instant specification and the art of record fail to teach that the other cell types recited in claim 6 have osseointegration activity. The instant claims are drawn to a genus of diverse cell types and integrin receptors. However, the specification teaches that only bone cells (osteoprogenitor cells) have osseointegration activity and that SEQ ID NO:15 binds integrin $\alpha_v\beta_3$ on osteoprogenitor cells. These teachings are not tantamount to SEQ ID NO:11 (or any other claimed osteopontin peptide fragment) binding any integrin receptor and causing attachment, spreading and osseointegration of any cell type.

At the bottom of page 12 to page 13 of the Brief, Appellant states that osseointegration is a complex process and involves wound healing and osteogenesis. Appellant argues that because of the ubiquitous expression of integrins on cells, and the fact that the specification clearly demonstrates the ability of the peptides to bind to at least one integrin on a cell surface, claim 6, reciting that the claimed peptides bind to at least one integrin receptor on a cell, wherein the cell is selected from the cells listed in

claim 6 is enabled. Appellant argues that a prima facie case of non-enablement can only be made upon a showing of evidence, not argument of why one skilled in the art would not be able to make and use the claimed subject matter. Appellant cites In re Wands. Appellant concludes this section by stating that the claims are enabled by Appellant's specification in view of the prior art.

The instant specification fails to provide an enabling disclosure as defined by the Wands Factors. The instant claims broadly encompass diverse cell types and integrin receptors. The specification only teaches that bone cells (osteoprogenitor cells) have osseointegration activity through the action of SEQ ID NO:15 binding integrin $\alpha_v\beta_3$ receptors on osteoprogenitor cells. This is not tantamount or predictive to the claimed osteopontin peptide fragments binding other integrins and it will not work if the cell does not express that integrin. It would require an indeterminate quantity of unpredictable experimentation for the skilled artisan to carry out the steps required to practice the full scope of the claims. This would require discerning whether all of the diverse cells types (as recited in claim 6) express the integrin receptors (as recited in claim 1) and if those cells (which express the integrin receptor) can bind the claimed osteopontin peptide fragments and induce osseointegration. The state of the prior art fails to provide evidence for the degree of predictability in the art, thus more direction is needed in the specification. Hu *et al.* teach that osteopontin binds integrin receptors $\alpha_v\beta_3$, $\alpha_v\beta_1$ and $\alpha_v\beta_5$, <u>not</u> all of the integrins as recited in instant claim 1. Even if osteopontin bound several integrins, it does not mean that the claimed peptide fragments will. In addition, neither the art of record or the specification teach other cell types that have

osseointegration activity. The biological function of the claimed osteopontin peptide fragments is osseointegration, not just attaching and spreading. Because the state of the prior art fails to provide predictability, the skilled artisan cannot readily anticipate the effects. The instant specification fails to provide working examples. The specification need not contain working examples if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable and/or undeveloped art. In the instant case, the specification only teaches that osteoprogenitor cells have osseointegration activity and that SEQ ID NO:15 binds integrin $\alpha_v\beta_3$ on osteoprogenitor cells.

Undue experimentation is a conclusion reached by weighing all of the Wands Factors. A considerable amount of time is permissible for the quantity of experimentation needed to make and/or use an invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and Applicant has provided no guidance. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

Regina M. DeBerry, Ph.D
August 10, 2006

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